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Colon capsule endoscopy: Current status and future directions

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Core tip: Colon capsule endoscopy is a promising, minimally invasive wireless technique for the visualization of the colon. With the second generation, the diagnostic accuracy of Colon capsule endoscopy has significantly improved for polyp detection. Preliminary data suggest that colon capsule endoscopy may be useful to monitor mucosal inflammation in patients with inflammatory bowel disease. Limitations include the inability to take biopsies and the procedural costs. However, given the potentially higher acceptance within an average risk colorectal cancer (CRC) screening population, its usefulness as a screening tool with regard to CRC prevention should be further evaluated.

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Abstract

Colon capsule endoscopy (CCE; PillCam Colon; Given Imaging; Yoqneam, Israel) is a minimally invasive wireless technique for the visualization of the colon. With the recent introduction of the second generation colon capsule the diagnostic accuracy of CCE for polyp detection has significantly improved and preliminary data suggest it may be useful to monitor mucosal inflammation in patients with inflammatory bowel disease. Limitations include the inability to take biopsies and the procedural costs. However, given the potentially higher acceptance within an average risk colorectal cancer (CRC) screening population, its usefulness as a screening tool with regard to CRC prevention should be further evaluated.

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Key words: Capsule endoscopy; Endoscopy; Colon capsule endoscopy; Colonoscopy; Colorectal cancer; Colon; Colonic capsule endoscopy; Inflammatory bowel disease

INTRODUCTION

Endoscopic screening for colorectal cancer (CRC) has been shown to be effective in reducing mortality from the disease^[1,2]. However, while the decrease in CRC mortality is primarily attributable to the use of colonoscopy, its acceptability is still low among patients. Therefore, less-invasive screening methods with comparable sensitivity for the detection of polyps and cancer are highly desired.

Colon capsule endoscopy (CCE) was first introduced in 2006 as a wireless, minimally invasive technique for the imaging of the large bowel that does not require sedation or gas insufflation^[3]. However, while capsule endoscopy of the small bowel has quickly found its place as a first-line imaging device for patients with obscure gastrointestinal bleeding, CCE was immediately met with skepti-

Table 1 Comparison of technical features of first and second generation colon capsules

CCE	Year of introduction	Size (mm)	Field of view	Frame rate (images/s)	Frame rate in the upper intestines	Special features
PillCam Colon 1 (CCE-1)	2006	31 × 11	156°	4	Sleeping mode 1 h 45 min	-
PillCam Colon 2 (CCE-2)	2009	31.5 × 11.6	172°	4-35	14/min until first frame of small bowel	Adaptive Image rate, Graphic interface, Live imaging

CCE-1: First generation colon capsule endoscopy; CCE-2: Second generation colon capsule endoscopy.



Figure 1 First and second generation colon capsules. CCE-1: First generation colon capsule endoscopy; CCE-2: Second generation colon capsule endoscopy.

cism due to high procedural costs, the need for extensive bowel cleansing in order to gain reasonable polyp detection rates and the inability to take biopsies, thus requiring additional conventional colonoscopy to confirm finding and remove polyps. To increase the accuracy of CCE, the second-generation colon capsule (CCE-2) was recently developed that has an increased angle of view for each of the two cameras involved allowing for a panoramic view and an adjustable frame rate ranging from 4 to 35 images per second^[4]. The increased demand for this CE-marked minimally invasive technique has recently prompted the European Society of Gastrointestinal Endoscopy (ESGE) to publish a consensus guideline on the standardized use of CCE^[5]. In February 2014, FDA approval has been granted for CCE basing on data from a 16-site clinical trial involving 884 patients that assessed the safety and effectiveness of CCE in detecting adenomas at least six millimeters in size^[6].

In this review, the current and future role of CCE, its indications and limitations will be discussed.

COLON CAPSULE ENDOSCOPY - TECHNICAL FEATURES AND SAFETY

PillCam colon capsule endoscopy (Given Imaging Ltd, Yoqneam, Israel) is now available in its second generation (CCE-2; Figure 1). CCE-2 is 11.6 mm × 31.5 mm in size and features two head cameras that each have a 172° angle of view, allowing for almost 360° visual coverage of the colon. While the first-generation colon capsule had a flat frame rate of 4 images per second only, CCE-2

comes along with an improved image acquisition and an adaptive frame rate from 4 to 35 images per second (Table 1). This means that the camera is able to capture up to 35 pictures while in motion whereas 4 images per second are captured when it is virtually stationary to save battery power. The transit time of the capsule from the small bowel into and through the colon is relatively long, and the battery power of the capsule must therefore not be overused. To transfer the capsule optimally through the small bowel and colon, a laxative (booster) is ingested to accelerate the transit of the capsule through the small bowel into the colon (hence the name booster). Automatic detection of the small bowel mucosa triggers the timing of booster ingestion and is signaled to the patient by the data recorder. This is optimized by the CCE-2 and new data recorder technique and this technical innovation has been shown to be highly reliable in clinical studies^[7].

The resolution of CCE-2 imaging is below 0.1 mm, with a magnification of about 1 to 8. Polyp size can be estimated with the graphic interface tool of the included Rapid 8™ software. This tool, however, has not yet been verified in patients. Additional software features such as the, Flexible spectral imaging color enhancement* (FICE) technology permit enhanced visualization of detected lesions.

CCE has so far been shown to be a safe procedure and complications were almost all attributed to bowel cleansing and/or performance of colonoscopy including therapeutic interventions. In the two prospective studies that have compared CCE-2 with conventional colonoscopy, adverse events were reported from 6.8% and 8% of patients, respectively^[4,8]. However, fatigue reported from two patients in the study by Spada *et al.*^[8] was the only adverse event directly related to the CCE procedure itself. An overview of reported adverse events is shown in Table 2.

BOWEL PREPARATION FOR COLON CAPSULE ENDOSCOPY

A thorough bowel cleansing procedure is indispensable for the success of CCE. Accurate polyp detection can only be achieved when the colon is completely free of solid stool because unlike in conventional colonoscopy, a washing or sucking device is not available. In addition, a clean bowel promotes capsule propulsion for a complete bowel investigation which otherwise has to rely on longitudinal large bowel contractions which only occur a few times each day. For a better description of bowel cleanli-

Table 2 Complication rates reported from studies involving both first and second generation colon capsules *n* (%)

Ref.	Year	<i>n</i>	Complications		Major complications in detail
			Minor	Major	
Schoofs <i>et al</i> ^[3]	2006	41	0	0	-
Eliakim <i>et al</i> ^[37]	2006	98	0	1	Perforation at colonoscopy
Van Gossum <i>et al</i> ^[10]	2009	320	26 (2.9%)	0	Associated to bowel preparation: 22/26
Eliakim <i>et al</i> ^[4]	2009	104	8 (7.7%)	1 (0.96%)	7/8 associated to bowel preparation 1/1 urinary retention
Pilz <i>et al</i> ^[38]	2010	59	1 (1.69%)	1 (1.69%)	1/1 perforation nach Koloskopie 1/1 skin reaction from capsule electrodes
Gay <i>et al</i> ^[39]	2010	128	0	0	-
Sacher-Huvelin <i>et al</i> ^[11]	2010	545	19 (3.5%)	3 (0.5%)	Heart failure, potentially associated to bowel preparation: patient died Bleeding at mucosectomy Perforation at colonoscopy
Spada <i>et al</i> ^[8]	2011	109	8 (6.8%)	1 (0.85%)	5/8 associated to bowel preparation 2/8 fatigue 1/8 pain 1/1 perforation at colonoscopy
Herrerías-Gutiérrez <i>et al</i> ^[40]	2011	144	0	0	-
Hartmann <i>et al</i> ^[13]	2012	50	4 (8%)	1 (2%)	3/4 associated to bowel preparation 1/1 perforation at colonoscopy
Kakugawa <i>et al</i> ^[14]	2012	64	1 (1.56%)	0	1/1 associated to bowel preparation
Total	-	1621	67 (4.1%)	8 (0.49%)	-

Most complications are suspected to derive from colonoscopy and/or bowel preparation regimen and not related to CCE. CEE: Colon capsule endoscopy.

Table 3 Four-point grading scale for objective description of the level of cleanliness of the colon during colon capsule endoscopy^[41]

Cleansing level scale	Description	Categories
Poor	Inadequate; Large amount of fecal residue precludes a complete examination	Inadequate
Fair	Inadequate but examination completed Enough feces or turbid fluid to prevent a reliable examination	Quality of the investigation is significantly compromised
Good	Adequate Small amount of feces or turbid fluid not interfering with examination	Adequate
Excellent	Adequate No more than small bits of adherent feces	Quality of the investigation is not significantly compromised

ness in clinical trials, a 4-point grading scale ranging from poor to excellent has been proposed (Table 3).

For optimal bowel preparation, the ESGE guidelines recommend a split-dose regimen of at least 4 L of polyethylene glycol (PEG) solution to be administered on the evening before and during the morning of the exam itself^[5]. This bowel cleansing preparation should be preceded by a clear liquid diet on the day before the procedure. More recently, a prospective, randomized study has shown equal efficacy of a one-day cleansing regimen *vs* a two-day protocol^[9].

There is ample evidence that boosters of low-dose sodium phosphate (NaP) should be added to the PEG-based bowel preparation to accelerate transit time and enhance capsule visibility (Table 4)^[10,11]. Currently, the recommended dose of NaP booster is 30 mL diluted with one liter of water to be taken when the capsule has entered the small bowel and a second booster of 15–25 mL NaP with 500 mL of water 3 h later if the capsule has not been egested by that time^[5]. Higher doses of NaP were associated with an increased risk of side effects and NaP should be avoided in elderly patients as

well as patients with hypovolemia, renal insufficiency, active colitis, and those taking specific medications including ACE inhibitors^[12].

Hartmann *et al*^[13] observed good cleanliness following PEG plus ascorbic acid as the booster but incomplete investigations in 24% of cases. Finally, Mg-Citrate has also been recommended as a booster in a recent investigation^[14]. Thus, a cleansing formulation with little or no toxicity and a broad patient tolerability still needs to be defined.

INDICATIONS AND CONTRAINDICATIONS FOR COLON CAPSULE ENDOSCOPY

The acceptance of conventional colonoscopy as a screening tool for colorectal cancer is generally low despite the fact that colorectal carcinoma associated mortality may be significantly reduced^[15,16]. Therefore, the main interest for CCE development was its use as a minimally invasive, widely accepted screening tool for polyp detection.

Table 4 Diagnostic accuracy of colon capsule endoscopy for the detection of significant colon polyps (≥ 6 mm or ≥ 3 polyps)

Ref.	Year published	Colon capsule	Number of patients included	Sensitivity	Specificity	PPV	NPV
Schoofs <i>et al</i> ^[3]	2006	CCE-1	36	77%	70%	59%	84%
Eliakim <i>et al</i> ^[37]	2006	CCE-1	84	50%	83%	40%	88%
Van Gossum <i>et al</i> ^[10]	2009	CCE-1	320	64%	84%	-	-
Gay <i>et al</i> ^[39]	2010	CCE-1	126	87.5%	76%	79%	85%
Pilz <i>et al</i> ^[38]	2010	CCE-1	56	79%	54%	63%	71%
Sacher-Huvelin <i>et al</i> ^[11]	2010	CCE-1	545	39%	88%	47%	85%
Eliakim <i>et al</i> ^[4] second gen	2009	CCE-2	98	89%	76%	46%	97%
Spada <i>et al</i> ^[8]	2011	CCE-2	109	84%	64%	-	-
Rex <i>et al</i> ^[6]	2013	CCE-2	689	81%	93%	-	-

CCE-1: First generation colon capsule endoscopy; CCE-2: Second generation colon capsule endoscopy; PPV: Positive predictive value; NPV: Negative predictive value.

Indeed, it was recently reported that screening participation increased by fourfold when CCE was offered as an alternative to conventional colonoscopy even with the knowledge that a later colonoscopy could be necessary^[17]. A number of prospective studies have compared CCE to conventional colonoscopy as the gold standard for the detection of significant polyps (polyp size ≥ 6 mm or ≥ 3 polyps), a widely accepted surrogate marker for advanced neoplasia (Table 4). Published studies that used the first generation colon capsule (CCE-1) for comparison with conventional colonoscopy reported sensitivities and specificities for the detection of significant polyps in the range of 39.0%-87.5% and 54.0%-88.0%, respectively. Two meta-analyses of CCE-1 studies involving 7 and 8 studies, respectively, have since been published^[18,19]. They showed overall sensitivities and specificities of 69% and 68% and 86% and 82%, respectively, for the detection of significant polyps.

With the introduction of the second-generation CCE-2 in 2009 and implementation of more standardized bowel cleansing protocols the detection of colonic lesions has significantly increased diagnostic accuracy. To date, two studies have been published on polyp detection by CCE-2 compared to conventional colonoscopy^[4,8] while a third study involving 884 patients has only been published in abstract form^[6]. For the detection of significant findings, sensitivities and specificities ranged from 81%-89% and 64%-93%, respectively. In the latter study which is the largest investigation of CCE-2 so far, a sensitivity of 88% (95%CI: 82%-93%) was found for the detection of adenomas ≥ 6 mm and 92% (95%CI: 82%-97%) for adenomas ≥ 10 mm with respective specificities of 82% (95%CI: 80%-83%) and 95% (95%CI: 94%-95%).

Finally, a recent study suggests that CCE-2 may be better at detecting flat lesions compared to conventional colonoscopy. In this retrospective analysis of 16 patients it was shown that 25 out of 27 flat lesions ≥ 6 mm detected with conventional colonoscopy were correctly detected by CCE-2. Where conventional colonoscopy categorized only 15 of these lesions as polypoid, CCE-2 classified 24 of these as polypoid. This discrepancy may have been caused by air insufflation during conventional

colonoscopy and it suggests that the currently widely used Paris classification for polyps may not be adoptable for CCE. The sensitivity and specificity for detection of flat lesions by CCE-2 in this study were 90% and 96%, respectively^[20].

Conventional colonoscopy represents the gold standard for the examination of the colon, and a complete investigation that includes visualization of the cecum and/or terminal ileum may be attained in over 95% of cases^[21], but may be as low as about 60% in some cohorts^[22]. In most of these cases, difficult anatomical conditions, bowel adhesions and previous surgical interventions result in incomplete colonoscopic examinations. Thus, CCE may play a particular role in patients who have undergone incomplete colonoscopy. Other indications may involve unwillingness to undergo conventional colonoscopy for personal or religious reasons and contraindications for sedation. A number of recent studies suggest that there is increased interest to study the usefulness of CCE in these heterogeneous patient groups.

In a recent French multicenter study, 72% of 102 patients were investigated by CCE-1 following incomplete colonoscopy and 28% for contraindications for colonoscopy^[23]. Overall, significant findings (carcinoma, inflammatory bowel disease, angiectasia, and others) were observed in 34% of cases and treatment decision was subsequently influenced in 59% of these patients. Several other studies have reported similar percentages of significant findings and influence on treatment decisions (Table 5). However, several reports of capsule retentions suggest that CCE should be used with caution on patients with suspected malignancies unable or unwilling to undergo conventional colonoscopy.

Mucosal healing as assessed by optical colonoscopy is increasingly employed as an endpoint in inflammatory bowel disease (IBD) treatment studies as well as in clinical practice^[24]. Monitoring of mucosal inflammation by CCE may play a role as a more widely accepted diagnostic tool to guide treatment decisions in IBD patients. Therefore, a number of recent studies have investigated the role of CCE in the assessment of mucosal inflammation^[25-29]. In the study conducted by Sung *et al*^[25], the sensitivity and specificity of CCE for the detection of active

Table 5 Colon capsule endoscopy for incomplete colonoscopy or patients with contraindications for colonoscopy

Ref.	Year	n	CCE	Complete visualization of the colon by CCE + colonoscopy	Treatment decision influenced in ...	Significant findings	Capsule retention
Pioche <i>et al</i> ^[23]	2012	102	CCE-1	93%	59%	34%	12 cases
Alarcón-Fernández <i>et al</i> ^[42]	2012	34	CCE-1	85%	59%	23.5%	-
Negreanu <i>et al</i> ^[43]	2013	67	CCE-2	77% (CCE) 90% (CCE + colonoscopy)	-	34%	2 cases
Triantafyllou <i>et al</i> ^[44]	2013	75	CCE-1	91%	-	44%	-

CCE: Colon capsule endoscopy; CCE-1: First generation colon capsule endoscopy; CCE-2: Second generation colon capsule endoscopy.

ulcerative colitis was 89% and 75%, respectively when compared to conventional colonoscopy. However, more recent studies showed that CCE was clearly inferior compared to conventional colonoscopy for the assessment of disease activity and extent^[26]. At present, conventional colonoscopy should therefore be the first choice to guide treatment decisions while the role of CCE in IBD needs further clarification.

Contraindications for CCE are similar to those defined for small bowel capsule endoscopy^[30]. These include swallowing disorders, prior abdominal surgery of the gastrointestinal tract, known or suspected bowel obstruction, presence of a cardiac pacemaker and pregnancy. So far, colon capsule retention has only been reported in studies involving patients with incomplete endoscopy or those who were unwilling or unable to undergo conventional colonoscopy and those with suspected gastrointestinal malignancies, inflammatory bowel disease or prior radiation history. In all but two patients, capsules could eventually be evacuated by flexible endoscopy without the need for surgery. In two cases reported by Negreanu and colleagues, surgery for bowel cancer was decided upon capsule findings and was subsequently performed without complications and the capsules were evacuated during the procedure. This, however, emphasizes the need to carefully select patients who can undergo CCE without the risk of complications. Finally, patients who are at risk of NaP toxicity should undergo alternative booster preparations such as Mg-Citrate^[5,31,32].

CONCLUSION

Colon capsule endoscopy has shown to be a feasible and exceptionally safe procedure for the visualization of the entire colon. Its acceptance among patients and accuracy for the detection of pathologic findings has been studied for a variety of indications including the detection of polyps and adenomatous lesions as well as for monitoring inflammatory bowel disease. With the introduction of the second-generation colon capsule the sensitivity of the procedure for polyp detection has been markedly increased when compared to standard colonoscopy, which is mainly explained by the improved optical setup. In addition, CCE may be useful in patients with ulcerative colitis to monitor disease activity. Finally, patients unable or unwilling to undergo conventional colonoscopy are currently the main focus of attention and the indication

for CCE should be discussed in these patients on an individual basis as outlined in the ESGE guidelines.

However, CCE is limited as a first-line diagnostic device due to the inability to take tissue samples and to predict histology upon polyp detection. Thus, patients in whom significant findings are made during CCE still need referral to colonoscopy for clarification. In addition, even the improved second-generation colon capsule holds a sensitivity that is short of 90% in comparison to conventional colonoscopy for the detection of significant findings. Some authors argument that conventional colonoscopy itself might be an imperfect golden standard and that CCE might surpass detection rate of colonoscopy in some instances^[33]: *e.g.*, limitations of CCE in study results may be explained by the mismatch of polyp-size estimation between CCE and conventional colonoscopy, which served as the gold standard in these studies. That is, polyps, which were “overestimated” in size by CCE, may in fact have been “underestimated” by colonoscopy. Thus, currently it remains unclear how CCE might find a place in CRC prevention in the long-term.

Finally, the overall accuracy of CCE largely depends on bowel cleanliness. Indeed, split-regimens based on polyethylene glycol with additional booster preparations to be administered during the procedure are required to obtain adequate bowel cleanliness. It was shown in several studies that a complete visualization of the bowel mucosa as well as high capsule egestion rate is preferably obtained with sodium phosphate boosters. The downside of this cleansing regimen is its responsibility for most of the adverse events during CCE. Another issue that needs further clarification is the cost-effectiveness of CCE in different indications. However, it has been suggested that CCE may be cost-effective in a CRC screening program if the uptake of CCE as a screening tool is higher than that of colonoscopy^[34]. Future approaches to CCE are aiming at the improvement of polyp characterization, mainly *via* improvement of the software setup for polyp size estimation and by integration of chromoendoscopy techniques and/or confocal imaging with near infrared light for virtual histologic characterization^[35,36]. In addition, externally rechargeable batteries or even battery-free capsules are being developed.

Taken together, CCE is a safe and feasible method for the minimally visualization of the colon. Current indications aim at patients in whom conventional colonoscopy cannot be or has been incompletely performed.

Given the poor acceptance of screening colonoscopy, CCE should be tested in large-scale screening programs. For patients unable to undergo conventional colonoscopy, randomized comparisons with other non-invasive imaging modalities (*e.g.*, virtual colonoscopy) are certainly required.

CONFLICT OF INTEREST

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